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Date: March 22, 2000

of Pages to Follow: 2

SUBJECT: Merck Sharp & Dohme/MRL Comments on CPMP/ICH/2711/99, Step 2 Draft Consensus Guideline, "Note for Guidance on Clinical Investigation of Medicinal Products in the Pediatric Population"

Dear Professor Bass,

Please find attached the comments from the MSD/MRL Pediatric Task Force.

Sincerely,

RB → REC

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LH/ASR

Bea Loran

Bea Loran
Director, Regulatory Affairs
Europe

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**Merck Research Laboratories (MRL) Comments
on CPMP/ICH/2711/99
ICH Topic E11
Clinical Investigation of Medicinal Products in the
Pediatric Population, Step 2 Draft Consensus Guideline**

Comment # 1**Page 8****2.3.1 Pharmacokinetic (PK) studies****(MRL strongly urges this comment be adopted) :**

MRL recommends that the word "bioequivalence" (BE) be changed to "relative bioavailability." (BA) Some useful and acceptable pediatric formulations may not achieve BE but if the relative BA were known, useful recommendations could be included in labeling to guide dosing of pediatric formulation in children.

Comment # 2**Page 11****2.3.1 Pharmacokinetic studies****Practical Considerations**

MRL suggests deleting the reference to "population PK" in the last major and first subbullet. A group of 5-8 children in a PK study cannot approximate a population. MRL suggests changing the second subbullet to "optimal sampling theory" (i.e., not population PK), although it should be noted (at the end of the section) that the utility of this approach assumes that kids are like adults (which will obviously not always be true and is the reason for the study in the first place).

Comment # 3**Page 13****2.3.3 Safety**

MRL suggests that the phrase "medicinal products to be used chronically" be deleted from the parenthetical list of products warranting evaluation with respect to growth and development, and that a new sentence be inserted after the parenthesis to read :

"In general, any medicinal product to be used chronically should also be evaluated."

The paragraph then reads :

"Depending upon the nature of the compound, (eg hormones, growth factors, or medicinal products with pre-clinical data suggesting effects on growth ; or medicinal products with central nervous system effects) special consideration

should be given on short and long term growth and development. In general, any medicinal product to be used chronically should also be evaluated.

Comment # 4**Page 17****2.4.4 Children (2-11 years)**

MRL suggests specifying that the discussion on page 17 applies only to medicines with a scientific rationale to consider such as those categories described on page 13.

Comment # 5**2.4.4 Children (2-11 years)**

MRL suggests adding a reference in 2-11 year old section whereby some of the issues outlined under the "adolescents" section are also considered in the older cohort of the 2-11 age-group. For example, cigarette use should be considered in older children and adolescents.